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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/375,246	08/16/99	PERUCHO M	P-LJ-3597

EXAMINER

HM12/1022

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ART UNIT	PAPER NUMBER
1655	10

DATE MAILED: 10/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev 11/00)

Application No.	Applicant(s)
09/375,246	Perucho et al.
Office Action Summary	
Examiner	Art Unit
Jehanne Souaya	1655

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 3, 2001*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Currently, claims 1-23 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining an increased or decreased risk of developing colorectal cancer by determining the relative change in the quantity of nucleic acids between cancerous and noncancerous cells, does not reasonably provide enablement for determining any clinical outcome of a subject with any cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are broadly drawn to determining any clinical outcome of a subject with any cancer by comparing the relative change in quantity of nucleic acids between cancerous and noncancerous cells. The specification teaches that genomic instability characterizes neoplastic transformation and generates tumor cell aneuploidy (p. 1). The specification teaches that AP-PCR DNA fingerprinting was applied to the analysis of chromosomal numerical changes in human colorectal cancer by measuring the genomic damage fraction of individuals (p. 15), and further teaches correlating GDF values in a method called amplotyping which showed that losses of sequences from chromosomes 1, 4, 9, 14, and 18 occurred in about 50% of the tumors from metastatic colon cancer. The specification, however, does not teach such studies with any other type of cancer and teaches that different cancers have been found to possess different gains and losses in different chromosomes.

The art is unpredictable as to determining a clinical outcome of any cancer. Vogelstein (Trends in Genetics, 1993, vol. 9, pp 138-141) teaches that each individual cancer arises not from a single mutation, but from the accumulation of several mutations (p. 138, col 1, lines 9-12). Vogelstein teaches that 3 to 7 "hits" are required for cancer to form, and that these hits could represent insults to separate cells, but because each cancer appears to arise from a single cellular progenitor, it is more likely that they represent sequential mutations of growth regulatory gene in a single cell and its progeny (p. 138, col. 1, 2nd para). Vogelstein further teaches that not all combinations of oncogenes (a gene whose activity leads to enhanced cell growth) will transform cells, suggesting that cells have evolved several growth control circuits and that more than one

circuit must be damaged before abnormal growth ensues (see p 139, col. 1, "transformation in vitro"). Vogelstein further teaches that the cellular environment can modulate the number of hits required for tumorigenicity (p. 139, col. 2, para 1). Vogelstein also teaches an example of a model for colorectal tumorigenesis (fig. 3) which shows a sequential set of mutations in growth regulatory genes that must occur before cancer develops. Vogelstein teaches that in another type of cancer, cervical cancer, progression of HPV-initiated cells to the fully malignant state requires additional hits in genes not yet identified (p 140, col. 2, 1st para). Thus the teachings of Vogelstein illustrate the unpredictability of the art as to what is known about the mechanisms of different cancers.

Therefore, based on the lack of guidance from the specification and the unpredictability of the art with regard to determining the clinical outcome of any type of cancer, the skilled artisan would require undue experimentation to practice the invention as broadly as it is claimed. To practice the invention, the skilled artisan would have to perform a study, measuring the GDF of patients with many different types of cancers to correlate a GDF with clinical outcome. Although the amount of experimentation is not in and of itself necessarily undue, the study performed by the skilled artisan to practice the invention would be replete with trial and error, and the results of such a study are unpredictable, thus constituting undue experimentation.

Response to Arguments

4. The response traverses on the following grounds. The response traverses that the specification teaches a method that can be used to determine the clinical outcome of a subject

with any cancer and provides exemplary teaching regarding using the methods to determine the clinical outcome of a subject with colorectal cancer. This argument has been thoroughly reviewed but was found unpersuasive. The claims as written broadly encompass determining the clinical outcome (that is whether the subject will have an increased or decreased risk of the recurrence of the cancer and/or an increased or decreased likelihood the cancer will become metastatic) of a subject with *any* cancer by determining the change in quantity of nucleic acids between cancerous and non cancerous cells, however the specification has only exemplified determining an increased or decreased risk of developing colorectal cancer by determining the relative change in the quantity of nucleic acids between cancerous and noncancerous cells. Given that the heterogeneity between different types of cancers in terms of genetic vs environmental factors, and loss and gain of nucleic acid sequences is well known in the art and that the specification teaches that different cancers have been found to possess different gains and losses in different chromosomes, it is unpredictable to extrapolate that the results taught in the specification with regard to colorectal cancer will be analogous with any type of cancer. For example the specification teaches (p 23) neither gains of chromosome 8 or 13 were events specific for metastasis but to precede it, while chromosome 4 losses and chromosome 6 gains were significantly associated to the metastatic stage. Furthermore, with regard to recurrence of disease (different clinical outcome than metastasis), the specification has only shown that loss in chromosome 4 is linked to a decrease in survival over time, however the specification does not teach whether gains in chromosome 6 are also associated with such a clinical outcome. Although

one of skill in the art would know how to perform the analysis, the results of such an analysis are unpredictable as it is unclear if the gains in chromosome 6 are linked to recurrence of disease. The examiner agrees that applicant has generally taught how to measure a change in quantity of nucleic acids in cells. However, as exemplified by the teachings in the specification, the analysis of such for determining clinical outcome for colorectal cancer is unpredictable in that certain changes in quantity of certain specific chromosomes are associated with one clinical outcome, while other changes in other specific chromosomes are associated with a different clinical outcome. Such results are unpredictable, and are a property of a specific cancer. The specification does not provide a predictable correlation such that the skilled artisan could apply the general method to any cancer without requiring trial and error. The results of such an analysis are unpredictable in light of the teachings in the art and the specification and are considered undue. The broadly claimed invention is an invitation to experiment, the results of which are unpredictable.

The response also traverses that applicant disagrees with the assertion in the office action that to practice the invention the skilled artisan would have to perform a study measuring the GDF of patients with many different types of cancers to correlate a GDF with a clinical outcome and that a GDF was correlated to a clinical outcome of colorectal cancer without requiring a determination of GDF for patients with many different types of cancers. This argument has been thoroughly reviewed but was found unpersuasive. Firstly, with respect to GDF, the specification teaches specific gains and losses of specific chromosomes and linkage to metastasis (fig. 6),

however the specification does not appear to teach a correlation between specific GDF values and a clinical outcome (see examples in the specification. The section on "determination of the status of gains and losses" does not appear to indicate a correlation between a specific GDF value and metastasis or likelihood of recurrence of disease). Secondly, although the specification teaches how to measure changes in nucleic acid quantity in colorectal cells, the specification does not teach a correlation between specific GDF values and other types of cancer, such as cancers of the breast, prostate, etc. The gains and losses of specific chromosomes taught in the specification are specific to colorectal cancer, and such patterns of gains and losses do not necessarily correlate to and are unpredictable with regard to breast cancer, for example. The broadly claimed invention is drawn to determining the clinical outcome for any cancer based on quantitative changes in nucleic acids between cancerous and non cancerous cells, however the specification has only taught such with regard to colon cancer. It is unpredictable as to the outcome of a similar analysis with regard to breast cancer for example, and such an analysis would require trial and error, which is considered undue.

The response also traverses that the unpredictability for cancer diagnosis allegedly described by Vogelstein is non-analogous to the claimed methods as any alleged unpredictability in identifying a particular mutation or combination of mutations involved in a particular cancer is not relevant to the claimed methods because the claimed methods do not require knowledge of particular sequences. This argument has been thoroughly reviewed but was found unpersuasive as the Vogelstein reference was cited as a general reference to show the unpredictability taught in

the art with regard to the linkage of specific cancers with specific genetic lesions. From the Vogelstein reference, one of skill in the art would be taught that different mechanisms appear to be responsible for colorectal cancer than for cervical cancer for instance. Given this general teaching of unpredictability and the teachings in the art and the specification that different cancers have been found to possess different gains and losses in different chromosomes (one could envision that such might be due to the loss of specific disease associated genes) it would be readily apparent to the skilled artisan that gains and losses in certain chromosomes in one type of cancer could not necessarily be extrapolated to a different cancer (ie: colorectal cancer vs breast or cervical cancer). Furthermore, it is unpredictable as to whether a certain GDF value correlated to colorectal metastasis for instance, could also be used to determine breast tumor metastasis, or whether a predictable correlation can even be found with a certain GDF value and breast tumor metastasis. Likewise, it is unpredictable as to whether a certain GDF value correlated to colorectal cancer recurrence (which the specification does not teach) could be used to determine likelihood of breast cancer recurrence, for example. Therefore, the rejection under 35 USC 112/1st paragraph is maintained.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. No claims are allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Thursday from 7:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Jehanne Souaya
Patent examiner
Jehanne Souaya
October 17, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600